REMARKS

Claims 56-117 are currently pending in the application. No new matter is added by this response. Applicants wish to thank Examiners Tran and Ponnaluri for the telephone interview conducted with Applicants' representatives on September 10, 2004. A summary of the issues discussed during the interview is incorporated into the following remarks.

Formal Matters

Priority

The Office Action states that no certified copies of the two priority applications (UK0015443.5 and UK0026099.2) were filed, and thus Applicants' claim for foreign priority has been denied until the certified copies are filed. To the contrary, Applicants filed certified copies of the two foreign priority documents on September 17, 2003, which were received and docketed by the Patent Office on September 25, 2003. A copy of the filing and the stamped return postcard are included herewith.

Claim Amendments

Claims 56, 78, and 86 are amended. Claims 78 and 86 are amended to remove their dependency from claims which have been withdrawn. Claim 56 is amended pursuant Applicants' telephone interview with Examiners Tran and Ponnaluri. The amendment to claim 56 is made solely for the purpose of clarifying the subject matter of claim 56, and is not made to further distinguish the claim over the prior art of record. As noted below, Applicants do not believe that any amendment to claim 56 is required to make the claim non-obvious over the cited prior art, and have made the amendment only to clarify the Examiner's understanding of the meaning of "continuous line." Support for the amendment is found throughout the specification, and at least at page 3, lines 21-27.

Rejection of claims 56-66 and 78-85 Under 35 U.S.C. §103(a)

The Office Action has rejected claims 56-66 and 78-85 under 35 U.S.C. §103(a) as being unpatentable over Buechler et al. (U.S. Patent 6,057,098) in view of Miller et al. (WO 99/39210)

and also in view of de Wildt et al. (2000, Nature Biochemistry, 18:989-994). Each of these rejections is addressed separately below.

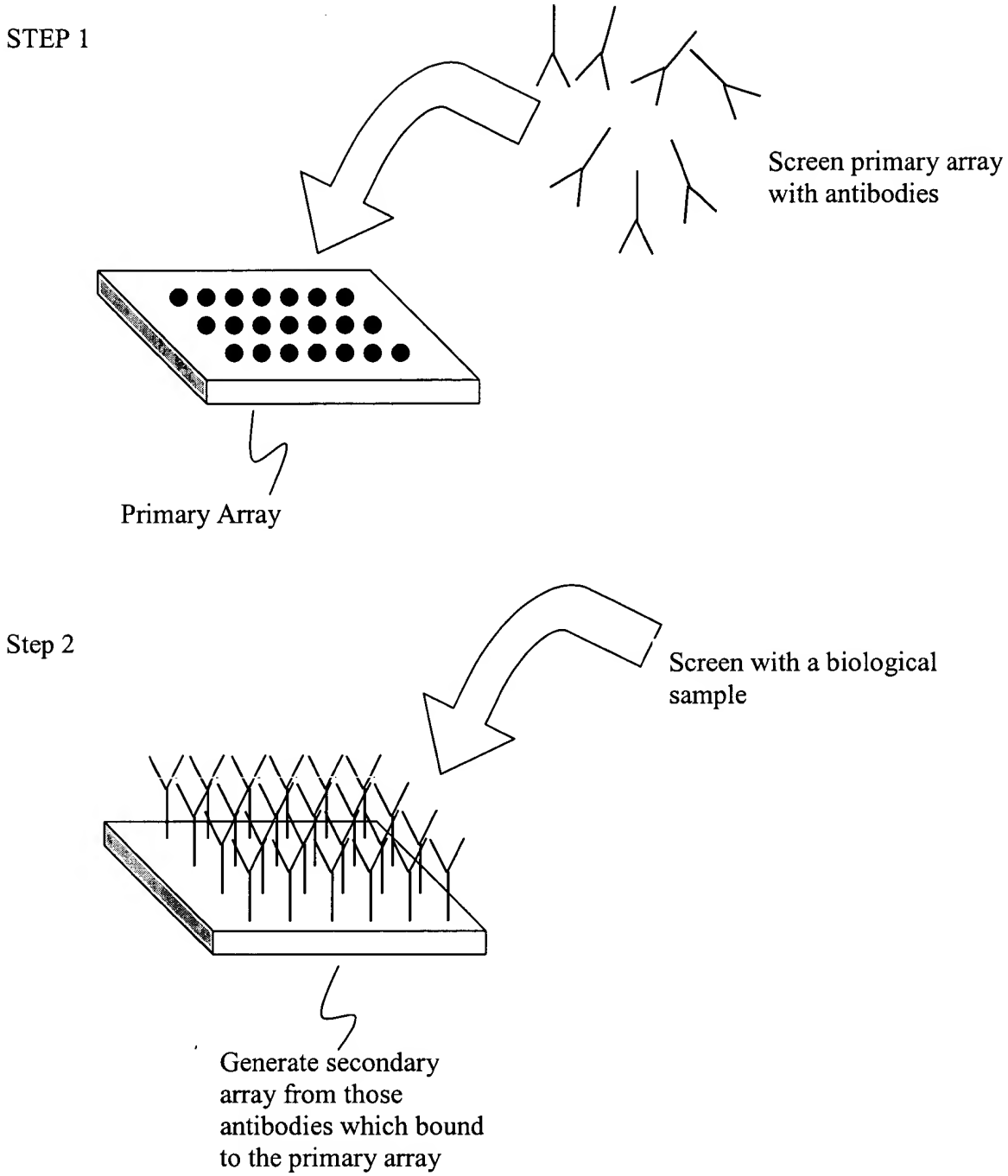
Buechler and Miller

The Office Action rejects the instant claims as being obvious over the combination of Buechler et al. and Miller et al. The Office Action asserts that Buechler et al. teach a method of producing a multivalent polypeptide display library that can be used in diagnostic tests, wherein the polypeptides comprise V_H or V_L. The Office Action notes, however, that Buechler et al. fail to teach that the polypeptide display library is applied to a solid surface. Applicants do not contest the Office Actions' characterization of the teachings of Buechler et al. The Office Action states that Miller et al. disclose a method for determining the protein profile of a biological sample comprising making a primary array of proteins wherein Xn is the coordinate along a first dimension of the array and Yn is the coordinate along a second dimension of the array. The Office Action states that Miller et al. teach screening the primary array with a plurality of antibodies and preparing the secondary array of antibodies that bind specifically to the proteins of the primary array, and then screening biological samples against the secondary array. The Office Action also characterizes Miller et al. as teaching a method of antibody screening using two high-density arrays wherein the primary array forms antigen-antibody complexes with the elements of the secondary array, and that Miller defines "array" as "including both linear and non-linear arrangements of a plurality of proteins." The Office action asserts that it would have been obvious to one of ordinary skill in the art to include the arrays of Miller et al. in the methods of Buechler et al., thus producing the claimed invention. Applicants respectfully disagree with the assertions of the Office Action and traverse the rejection.

As previously stated, Applicants do not disagree with the interpretation of the teachings of Buechler et al. set forth in the Office Action. Applicants maintain, however, that the teachings of Buechler et al. and Miller et al., taken alone or together do not teach arranging a first repertoire in at least one series of continuous lines such that each line of said series comprises a member of the first repertoire and arranging a second repertoire in at least one series of continuous lines such that each line of said series comprises a member of said second repertoire

such that the first and second repertoires form an array, such that a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire, and thus the references do not render the claimed invention obvious.

Miller et al. teach a **two-step method** for determining the protein profile of a cell. In the first step, a primary array is created comprising protein elements which mimic the antigenic diversity of a cell. The Office Action correctly states that Miller et al. teach that the array can be a linear arrangement of proteins. Applicants submit however, that a "linear" arrangement of proteins is not the same as a repertoire of polypeptides arranged in at least one first and at least one second series of "continuous lines." Miller et al. teaches that the primary array is screened with antibodies "one at a time." That is, the primary array is reacted with only one antibody molecule at any given point in time. Moreover, the Miller et al. antibodies are applied directly to the primary array, and any unreacted material is washed away. The antibodies themselves are applied in solution, not in the form of an array. Once antibody molecules are identified which bind to proteins of the primary array, the second step of Miller et al. teach that the binding antibodies are used to generate a secondary array. The secondary array is then screened against one or more biological samples to identify proteins in the biological sample which are bound by the arrayed antibodies. The biological sample is applied in solution, not in the form of an array. Thus, according to the teachings of Miller et al., the only arrays which are formed are the primary and secondary arrays, which are generated in sequence. Thus, the repertoires of the Miller et al. assays are never "juxtaposed", as required by Applicants' claims. The teachings of Miller et al. are summarized in the following schematic diagram:



"Continuous Lines"

During the telephone interview with Applicants' representative on September 10, 2004, the Examiner questioned the meaning of a "continuous line" was in the context of the claimed

invention. The Examiner believes that a "continuous line" may be taken to mean a series of spots which are arrayed in such close proximity that adjacent spots are in contact, thus forming a continuous line. This assertion is apparently in response to Applicants' remarks in their response of January 2, 2004, in which Applicants argued that neither Miller et al. nor de Wildt et al. taught "continuous lines", but instead taught discontinuous spots. Applicants submit that the specification clearly delineates the distinction between continuous lines and the spotted arrays taught by Miller et al. (and de Wildt et al.). The specification teaches on page 15, lines 3-7, that

> "[the method of the invention] contrasts with screening protocols in the prior art, whereby discontinuous spotting or compartmentalised wells are used to segregate individual combinations of molecules. In the present invention, continuous lines...intersect one another such that individual combinations or molecules exist at their points of intersection, or nodes."

Thus, the specification clearly distinguishes between a continuous line and a series of spots; they are not the same thing. While the Examiner is correct that a series of liquid spots may be placed so close together that adjacent spots coalesce to form a continuous line, Applicants submit that this is irrelevant, because none of the cited prior art teaches making a continuous line in this manner. Moreover, even if one were to erroneously construe the cited prior art as teaching continuous lines, none of the references teach "arranging a first repertoire in at least one series of continuous lines wherein each line of said series comprises a member of the first repertoire and arranging a second repertoire in at least one series of continuous lines wherein each line of said series comprises a member of said second repertoire wherein the first and second repertoires form an array, and wherein a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire," as required by the claims. There is nothing in Miller et al. that teaches members of a first and second repertoire, **each arranged in at least one series of continuous lines**, such that members of the first repertoire are juxtaposed to members of the second repertoire.

The Examiner suggested during the telephone interview that, although Miller et al. does not teach arraying molecules in a continuous line, one practicing the methods of Miller et al. *could* array the spots so close together that the spots coalesce to form a line. Applicants submit that there is no teaching in Miller et al. to suggest creating an array in this manner. To the

contrary, Miller et al. teach arraying proteins or antibodies such that each protein or antibody has an XnYn designation on the array which facilitates the identification of protein molecules in a biological sample by permitting one to refer back to the coordinates of the protein in the primary array. To "blend" or coalesce the spots of Miller et al. to form a continuous line would thus defeat the utility of Miller et al.; that is, having uniquely defined coordinates for *each spot*, thus permitting one to use the specific coordinates of each spot to determine the identity of proteins in the biological sample. Modification of Miller et al. to achieve the coalesced continuous lines suggested by the Examiner would thus modify the principle of operation of Miller et al. It is well settled that the Examiner is not permitted to read such modification into the reference. See, e.g., *In re Ratti*, 270 F.2d 810 (CCPA 1959).

Even if Miller et al. is taken to teach that the first and second arrays are produced as series of continuous lines, which Applicants maintain that it does not, there is no teaching in Miller et al. that members of the primary array are juxtaposed to members of the second array while arranged as continuous lines. Alternatively, if the primary array of Miller et al. is taken to be analogous to a first repertoire as claimed, and the antibodies screened against the primary array are taken to be analogous to a second repertoire, there is clearly no teaching in Miller et al. that either the primary array or the antibodies which are screened against the primary array are arranged in continuous lines. Alternatively, if the secondary array of Miller et al. is taken to be analogous to a first repertoire as claimed, and the biological sample to be screened against the secondary array is taken to be analogous to a second repertoire, there is still no teaching in Miller et al. that either the secondary array or biological sample is arranged in a series of continuous lines. Thus, there is no reading of Miller et al. which provides arranging a first and second repertoire in at least two series of continuous lines to form an array, such that a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire.

Even if combined with the teachings of Buechler et al., the combination does not read on the claimed invention. Thus, the combination of Buechler et al. and Miller et al. to not render the present invention obvious because the references, taken alone or together, do not teach each element of the claimed invention. See, e.g., *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974) (Holding that the prior art reference (or references when combined) must teach

or suggest ***all the claim limitations***). Accordingly, Applicants request that the rejection be reconsidered and withdrawn.

Buechler and de Wildt

The Office Action rejected claims 56-68 and 78-86 under 35 U.S.C. §103 as being obvious over the teachings of Buechler et al., in view of deWildt et al. (Nature Biochemistry, 2000, 18:989). The Office Action asserts that deWildt teaches a method for screening antibody-antigen interactions, whereby many antibodies are screened in parallel against many antigens by a filter screening technique which involves the use of ordered arrays of antibodies generated by robot picking and gridding. The Office Action asserts that one of skill in the art would have been motivated to combine the teachings of Buechler et al. and de Wildt et al. because the molecules of Buechler et al. could be applied in the high throughput assays of de Wildt et al. comprising polypeptides applied to a solid support without "sticky" or cross reactive colonies (citing de Wildt et al. abstract). Applicants submit that the Office Action has failed to establish a *prima facie* case of obviousness, because even if the teachings of both Buechler et al. and deWildt et al. were to be combined, one of skill in the art would not arrive at the claimed invention.

Buechler et al. has been discussed above, and Applicants acknowledge that Buechler et al. teach double chain antibody libraries. The Office Action states that de Wildt et al. disclose a method of gridding antibodies "in a 4x4 pattern on a first square filter (**row of spots**)" (emphasis added). Thus, the Office Action acknowledges that the array taught by de Wildt et al. is a row of spots; a row of **spots** is not a **continuous line** as required by the instant claims. Applicants turn the Office's attention to Figure 1A of de Wildt et al which shows clearly that the arrayed antibody molecules are in the form of spots on a surface, and are not in the form of a continuous line. According to the method taught by de Wildt et al., a second filter is *coated* with a binding partner for the arrayed (spotted) antibody library (specifically, BSA, ubiquitin, recombinant bacterial lysate or Protein-L; page 993, second column, second paragraph). The second filter is then placed in contact with the spotted colonies on the array, and an interaction between the

arrayed antibodies and the binding partner coated on the second filter is detected. Again, de Wildt teaches one array of spots of antibodies in contact with a membrane *coated* with ligand.

During the telephone interview with Applicants' representatives, the Examiner asserted the same rationale outline above for Miller et al., that is, that the spots taught in de Wildt et al. could be arrayed close enough so that they coalesce to form a continuous line. Again, Applicants emphasize that in order to render a claim obvious, all the claim limitations must be taught or suggested by the prior art. *Id.* As can be clearly seen from Figure 1A, the antibody libraries of de Wildt are arranged in a 4x4 array of discrete spots which do not contact one another. There is no teaching in de Wildt to array the antibody molecules in a manner which would permit them to come into contact, or to coalesce to form a line.

Even if the teachings of de Wildt were improperly carried out so as to spot the array in a series of coalesced spots (thus forming a line), Applicants submit that de Wildt still does not teach "arranging the first repertoire in at least one series of continuous lines wherein each line of said series comprises a member of said first repertoire and second repertoires in at least one series of continuous lines wherein each line of said series comprises a member of said second repertoire wherein the first and second repertoires form an array". de Wildt only teaches forming an array from an antibody library (analogous to a first repertoire) and then contacting that array with a membrane filter which is coated with a single ligand. There is no teaching of a second repertoire arranged in a series of continuous lines such that members of the first repertoire are juxtaposed to members of the second repertoire.

Applicants submit further that, similar to Miller, modification of the teachings of de Wildt et al. according to the Examiner's suggestion (that is, arranging the antibody library in an array such that individual spots coalesce to form a continuous line) would destroy the principle of operation of de Wildt and is therefore improper. de Wildt et al. identify members of the spotted antibody library which bind to the target ligands based on the identification of a binding signal generated from a given spot. If the spots were to be blended or coalesced as suggested by the Examiner, then one of skill in the art, practicing the method of de Wildt would not be able to determine which antibody library member was actually binding to the target ligand because the

distinction between members of the library would be corrupted. As noted above, this type of revision of the prior art is not permitted in an attempt to establish a *prima facie* case of obviousness.

The Office Action curiously emphasizes that the instant specification teaches that an example of a configuration of continuous lines which may be used according to the invention are "concentric circles". The Office Action fails to appreciate however, that the phrase "concentric circles" is not recited in the specification in isolation, but is part of a larger phrase which recites "concentric circles or polygons, used together with a star of radial lines" (page 3, lines 7-13). Regardless of whether the Office Action was pointing out the mere phrase "concentric circles" or the full phrase as recited in the specification, Applicants are unclear of the phrase's importance to the rejection set out in the Office Action. de Wildt et al. does not teach a repertoire arranged in a series of concentric circles, and moreover, does not teach a repertoire arranged in a series of concentric circles used together with a star of radial lines. The only thing Applicants can surmise regarding the Office Action's emphasis on this particular arrangement of continuous lines is that the Office Action may be referring to the circles present in, for example, Figure 1 of de Wildt et al. Applicants note however, that these circles are drawn on the figure by the authors to indicate which of the antibodies on the array were scored as being reactive with antigen. For example, the figure legend for Figure 1 states that "BSA-specific antibodies are circled". This does not mean that the antibodies are in the form of a circle, but that the circle was merely used to identify positive results (similarly, Figure 2 states that "D, M, or T-specific antibodies are circled"). Applicants thus submit that there is no teaching in de Wildt et al. of arranging a first repertoire in at least one series of continuous lines such that each line of said series comprises a member of the first repertoire and arranging a second repertoire in at least one series of continuous lines such that each line of said series comprises a member of said second repertoire such that the first and second repertoires form an array, such that a plurality of members of the first repertoire are juxtaposed to a plurality of members of the second repertoire, as required by the instant claims.

Accordingly, Applicants believe that the present claims are not obvious over the teachings of Buechler et al. and de Wildt et al. because, the teachings of these references, even if

combined, do not provide each element of the claimed invention. Applicants, therefore, request that the rejection be reconsidered and withdrawn.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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Name: Kathleen Williams
Registration No.: 34,380
Customer No.: 29933
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel.: (617) 239-0100